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CONTEMPORARY PROGNOSIS OF TRANSIENT ISCHAEMIC ATTACK PATIENTS:

A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background

Transient ischaemic attacks (TIAs) are common and place patients at risk of subsequent stroke. The 2007 EXPRESS and SOS-TIA studies, demonstrated the efficacy of rapid treatment initiation. We hypothesised that, with these findings having informed subsequent TIA management protocols, TIA prognosis in contemporary (2008 and later) patient cohorts would be more favourable than in historical cohorts.

Methods

A systematic review and meta-analysis of cohort studies and RCT placebo-arms of TIA (published 2008-2015). The primary outcome was stroke. Secondary outcomes were mortality, TIA and myocardial infarction. Studies were excluded if the outcome of TIA patients was not reported separately. The systematic review included all studies of TIA. The meta-analysis excluded studies of restricted TIA patient types (e.g. only patients with AF). The pooled cumulative risks of stroke recurrence were estimated from study-specific estimates at 2, 7, 30 and 90 days post-TIA, using a multivariate Bayesian model.

Results

We included 47 studies in the systematic review and 40 studies in the meta-analysis. In the systematic review (191,202 patients), stroke at 2-days was reported in 13/47 (27.7%) of studies, at 7-days in 20/47 (42.6%), at 30-days in 12/47 (25.5%) and at 90-days in 33/47 (70.2%). Studies included in the meta-analysis recruited 68,563 patients. The cumulative risk

of stroke was 1.2% (95% Credible Interval (CI) 0.6-2.2), 3.4% (95% CI 2.0-5.5), 5.0% (95% CI 2.9-8.9) and 7.4% (95% CI 4.3-12.4) at 2, 7, 30 and 90 days post-TIA, respectively.

Conclusion

In contemporary settings, TIA prognosis is more favourable than reported in historical cohorts where a meta-analysis suggests stroke risk of 3.1% at 2-days.

Text

Introduction

Transient ischaemic attacks (TIAs) are common and place patients at risk of subsequent stroke.(1) Given the considerable potential for mortality and serious morbidity related to stroke, the risk of stroke following TIA is a major health issue. In contemporary practice, with emerging diagnostic techniques and with revised guidelines incorporating evidence for rapid management policies and use of risk stratification strategies, TIA can be diagnosed and managed early. Landmark studies (EXPRESS and SOS-TIA)(1, 2) demonstrated that urgent evaluation and commencement of therapy markedly reduces the risk of stroke. With implementation of these findings in clinical practice, it may be expected that TIA prognosis in patients engaging with contemporary health care systems would be more favourable than in historical cohorts. We sought to test this hypothesis.

Methods

We conducted a systematic review of prospective and retrospective cohort studies (hospital-based and community-based cohorts) of TIA, plus placebo arms of Randomised Controlled Trials. We defined contemporary practice as practice reported in studies published in the post-EXPRESS /SOS-TIA (post 2007) era. Thus, we included studies published from 2008 to 2015. The outcomes of interest were stroke, recurrent TIA, myocardial infarction and mortality.

Search strategy and screening process

The search was conducted using the electronic databases Ovid Medline, Cochrane Library and Embase. Search limits used were English language, human and 2008-current. The search terms used were: [TIA (OR) ischaemic attack, transient (OR) amaurosis fugax] AND [outcome (OR) prognosis (OR) follow-up (OR) cohort (OR) randomised control trial (OR) risk (OR) natural history].

The last database search was conducted on 2nd June 2015.

Duplicate results of the search were removed and the abstracts were screened and assessed for eligibility. Following screening of abstracts, full-text copies of potentially eligible papers were retrieved and assessed for eligibility. The abstracts, methods and outcomes for each study were assessed for eligibility separately by two researchers (NN and PM) and any cases of disagreement were adjudicated by a third researcher (CL).

Reference studies of included papers were searched for relevant studies. Papers published prior to 2008 were excluded. While acknowledging that papers published later than 2007 may still include patients recruited prior to 2007, this provided an identifiable marker of (post-EXPRESS/SOS-TIA) contemporary TIA practice.

Inclusion criteria Prospective and retrospective cohort studies (hospital-based and community-based cohorts) of TIA were included. In addition to this, placebo-arms of randomised control trials were also included. The study factor was TIA and so studies of stroke and TIA were included only if TIA was reported separately. The primary outcome factor was stroke and secondary outcome factors were recurrent TIA, myocardial infarction and death. Studies reporting these outcomes were included. We included in the systematic

review all studies of TIA even if the entry criteria for the studies were restricted (eg. only patients with AF). However, we restricted our meta-analysis to studies with no restriction on the type of TIA patients.

Exclusion criteria Studies with outcomes only at time-points less than 48 hours post-TIA were not included in the systematic review. We excluded studies of both stroke and TIA, if the outcome of TIA patients were not reported separately.

For the meta-analysis, studies which included (on the basis of study population selection) only higher-risk or only lower-risk patient populations were excluded. These excluded studies were: those which defined TIA according to the tissue-based definition rather than the traditional World Health Organisation (WHO) time-based definition, studies which excluded AF patients, studies which included only patients undergoing CEA and studies which had a restricted patient age group.

TIA definition: The definition of TIA was by each individual study (either standard WHO definition or tissue-based definition).

Outcome definitions: The primary outcome of interest was stroke and we accepted each study's stroke definition. Similarly, we accepted each study's definition of secondary outcomes of myocardial infarction and death.

The meta-analysis was performed only with stroke as the outcome factor.

Data extraction

The PRISMA 2009 criteria were followed. In studies including patients with both TIA and stroke, with the outcome for TIA patients not reported separately, the corresponding author was contacted and specific TIA data was requested.

Extracted information from each article included: title, author, publication year, journal, period of data collection, source of TIA diagnosis (eg. ED physician, neurologist), definition of TIA (WHO time-based or tissue-based definition), country/countries where the study was conducted, study population (eg. ED, hospital in-patient), study participant limitations (eg. gender), clinical limitations (eg. carotid stenosis, AF), number of TIA participants at baseline, number of TIA participants analysed, study outcomes (in addition to stroke), method of outcome ascertainment, type of study (prospective/retrospective cohort, RCT), duration of follow-up and results (stroke, mortality, TIA and MI). Data extraction was independently performed by two researchers (NN, PM and CE). Any cases of disagreement were adjudicated by a third researcher (CL).

Statistical Analysis

Meta-analysis: We conducted a meta-analysis of 40 studies (33 prospective studies, 7 retrospective studies) with outcome factor stroke. The time-points of interest for cumulative risk of stroke recurrence are at 2, 7, 30 and 90 days post-TIA. We aimed to estimate the pooled cumulative risk of stroke recurrence at each time point.

A standard meta-analysis of the risk at each time point is problematic since the same studies do not contribute data at each possible time-point; as such, estimates of the pooled cumulative risk at each time-point are not guaranteed to be non-decreasing since the within-study correlation of estimates are ignored. We utilise a model for the multivariate (joint)

analysis of all studies at every available time point. In this approach, information is borrowed from studies that contribute to multiple time-points, improving the precision of the estimates, and the cumulative probabilities of stroke are explicitly constrained to be non-decreasing. We have utilised the Bayesian model presented in Jackson *et al*.(3) Briefly, the probability of stroke at each study for each period is modelled on the log-odds scale to be the sum of the unconditional log-odds of stroke at each time point (averaged across sites) and a study specific random effect (to model between study heterogeneity), assumed to follow a multivariate normal distribution. The unconditional probability of stroke at each time point (averaged across sites) is the parameter of interest, reflecting the pooled cumulative risk at each time-point. To complete the Bayesian model, uninformative prior distributions were placed on all model parameters; a Wishart prior was used for the covariance matrix of the random effect, and normal distributions (zero mean and variance of 1000) were used for the four time-specific unconditional log-odds parameters.

Bayesian inference was implemented via Markov Chain Monte Carlo simulation using the WinBUGS software(4) where we took 500,000 simulations from the posteriors joint distribution, allowing for a burn-in period of 50,000 simulations. Pooled cumulative stroke risks are summarised from the posterior distribution as the mean with 95% credible intervals given as the 2.5 and 97.5 percentiles. Convergence was assessed through inspecting trace plots of the MCMC simulated values, and running two MCMC chains to assess convergence using the Gelman-Rubin diagnostics. Data manipulation, summarizing and graphing was performed using R V3.3 software.(5)

Results

Study selection

Databases searching yielded a total of 4304 publications. After excluding duplicate records and screening, 130 full-text articles were retrieved and assessed for eligibility. Eighty-three of these studies were excluded. Five RCT placebo arms met our inclusion criteria but were not included as the authors did not respond to our request for additional data. The remaining forty-seven studies met the inclusion criteria and were included in the systematic review. We included forty studies in the meta-analysis.

Systematic Review

Characteristics of studies/data: Forty-seven studies (N=191,202 patients) were included in the systematic review. The study characteristics are summarised in supplementary table 1. In all 47 studies, the patients had a TIA as an index event at baseline.

Diagnosis: The diagnostic criteria for TIA were the time-based WHO definition (32/47 (68.1%) of the studies) or tissue-based definition (3/47 (6.4%) of the studies). In 12/47 (25.5%) of studies, TIA definition was not reported. We assumed a standard WHO time-based definition in these studies. In 25/47 (53.2%) of studies, the TIA diagnosis was made by a neurologist. ED physicians and stroke physicians made the diagnosis in 6/47 (12.8%) and 3/47 (6.4%) of studies, respectively. In 1/47 (2.1%) of studies, a physician made the diagnosis. Vascular neurologists made the diagnosis in 2/47 (4.3%) of studies. In 10/47 (21.3%) of studies it was not reported who made the diagnosis.

Study population: The admission criteria and patient population were also different among studies. In 19/47 (40.4%) of studies, the study population were non- selected ED care/ all comers. Hospital in- patient admission with a clear admission policy (study participant limitations such as age, gender, MRI/MRA on admission, carotid stenosis and admission within either 24 hours or 48 hours of symptom onset) accounted for 8/47 (17%) of studies, whereas 9/47 (19.1%) of studies included in-patient hospital admissions but without a clear admission policy or with admission policy not stated. In 2/47 (4.3%) of the studies, the patients referred to a stroke clinic were included in the study and 2/47 (4.3%) of the studies had patients from a TIA clinic. In 2/47 (4.3%) of studies, included patients from ED (attended by neurologist) and there were 2/47 (4.3%) community studies. In 2/47 (4.3%) of the studies, the location of the study population was not reported and in 1/47 (2.1%) of the studies had unclear study population.

Outcome reporting: Stroke at 2-days was reported in 13/47 (27.7%) of studies, at 7-days in 20/47 (42.6%), at 30- days in 12/47 (25.5%) and at 90-days in 33/47 (70.2%).

TIA was reported in 15/47 (31.9%) of studies, mortality in 19/47 (40.4%) and MI in 9/47 (19.1%). Unlike for stroke, for TIA, MI and mortality reporting was often not at consistent time points (such as at 2-days, 7-days, 30-days and 90-days), making calculation of summary statistics problematic. The follow-up period varied between studies (from 72 hours to 13.8 years) and varied even within studies for different outcomes (refer to supplementary table 1 for individual studies).

Meta-Analysis

The 40 studies included 68,563 patients. The MCMC chains from the Bayesian multivariate meta-analysis model appeared to converge to stable distributions after excluding the first

50,000 simulations, summaries of the posterior distributions for cumulative risks at each time-point are provided in Table 1. The study specific stroke risks at each time point are plotted together with estimates of the pooled risks in Figure 2, where each dot represents an individual study.

Discussion

Summary of main findings

The systematic review displayed variability in definition of TIA and clinical status of a person making the diagnosis of TIA. A few studies had markedly restricted study populations. While there were differences in study populations' location of care and service model between studies, the participants were almost all managed in secondary care rather than primary care.

The meta-analysis of 40 studies showed a cumulative risk of stroke of 1.2%, 95%CrI[0.006,0.022]at 2 days, 3.4%, 95%CrI[0.02,0.055] at 7 days, 5.0%, 95%CrI[0.029,0.082] at 30 days and 7.4%, 95%CrI[0.043,0.124] at 90 days.

Comparison with previous studies*(pre-EXPRESS/SOS-TIA)*

The early Oxfordshire study (1981-1986) reported stroke risk of 8.6% at 7-days and 12.0% at 30-days post-TIA.(6) The Greater Cincinnati/Northern Kentucky Stroke Study (1993-1994) reported stroke risk of 14.6% after TIA.(7) The California study (1997-1998), reported 90-days stroke risk of 10.5%.(8) A Canadian study (1999-2000) reported 90 days stroke risk as 9.5%.(9) In Northern Portugal (1998-2000), the 7-day stroke risk was found to be 12.8%.(10)

A small number of pre-EXPRESS studies reported stroke risk equivalent to, or less than in, our meta-analysis. An ED based study in Canada (in 2000) reported 30-day stroke risk of 5%.(11) In another study conducted in France (2003-2005), of patients admitted to the stroke unit, the stroke risk at 1 week and 3 months was found to be 2.5% and 3.5%, respectively.(12)

A systematic review and meta-analysis published in 2007, however found stroke risk of 3.1% at 2-days (compared to 1.2% in our meta-analysis) and 5.2% at 7-days (compared to 3.4% in our meta-analysis) and lowest risks were seen among patients treated in specialist stroke services.(13)

Thus, recurrent stroke-risk in these 'pre-EXPRESS/pre-SOS-TIA' studies was generally greater than (often considerably greater than) than the stroke-risk in our meta-analysis.

Stroke risks in our meta-analysis were greater than in SOS-TIA and in 'phase 2' of EXPRESS. In SOS-TIA (2003-2005), 90-day stroke risk was 1.24%(2) In EXPRESS (2004-2007), the 90- day stroke risk decreased from 10.3% in phase 1 to 2.1% in phase 2.(1) Stroke risk in our meta-analysis was also greater than in a large study reported subsequent to our review and meta-analysis (see below).(14)

Interpretation of the findings

We have found that, compared to findings in pre-EXPRESS historical cohorts, our meta-analysis of studies in more contemporary health settings reported lower rates of stroke following a TIA.

In 'optimal' contemporary practice, Amarenco et al's recent multi-site study (2009-2011) published in 2016 (subsequent to our review) found that stroke rates following a TIA or minor stroke at 2, 7, 30 and 90 days were 1.5%, 2.1%, 2.8% and 3.7%, respectively.(14) That

is, lower rates than in our meta-analysis. This study was conducted (like EXPRESS and SOS-TIA) in highly specialised settings where urgent evaluation and management of TIA was implemented via protocols in accordance with evidence-based best practice care.

Thus, we have demonstrated a gradient of highest stroke risk post-TIA in findings from 'historical' cohorts (highest risk), to the findings of 'post-EXPRESS' cohorts included in our meta-analysis, to the findings of a 'contemporary best-practice' cohort (lowest risk).

The defining characteristic of clinical practice (reflected in evidence-based clinical guidelines) (15-17) contemporaneous with this gradient in findings is decreasing time from incident event to initiation of management. Treatment modalities were largely unchanged.

Strengths and limitations

Strengths:

A strength of this systematic review and meta-analysis is the large number of studies from across a wide range of (secondary care) health care settings from around the world. In the 47 studies included in the systematic review, there were 191,202 patients, with 68,563 patients included in the meta-analysis.

Limitations:

An important limitation is a time lag in introduction of system change in TIA care, data collection and publication. Our sample population of studies included some patients who received treatment before the EXPRESS/S0S-TIA studies' publication (i.e. pre-2007). This together with different patient population and different health systems' approaches (not always informed by EXPRESS/SOS-TIA findings), makes our sample population highly heterogeneous. Hence, an appreciable proportion of patients in our systematic review and meta-analysis would not have received what is considered optimal care post-EXPRESS/SOS-

TIA. This, however, would have biased our findings towards the null, i.e. less difference in stroke-rates between historical and post-EXPESS studies. Our results remain robust from this viewpoint.

Secondly, there is a difference in ascertainment of study factor (TIA) in different studies. The case ascertainment method varied across studies. Most studies diagnosed TIA as per the time-based WHO definition while some studies followed the tissue-based definition. Studies explicitly employing tissue-based definition of TIA were however, excluded from our meta-analysis.

Additionally, there was heterogeneity in clinicians making the diagnosis of TIA, ranging from stroke physicians to ED physicians to ED residents.(18) Given the frequent difficulty of TIA diagnosis, there is potential for differences in diagnostic accuracy between included studies.(19)

Implications for practice and policy

A consideration of our findings in the context of previous literature and changes in evidence-based clinical guidelines suggests that the poorer prognosis in historical population contrasted with findings of more contemporary populations may be due to TIA patients being treated less intensely in historical cohorts. Furthermore, the results of the study conducted in expert tertiary stroke care centres and published in 2016,(14) suggest that with closer adherence to contemporary best practice, even better prognosis of TIA can be achieved. This difference suggests that clinical expertise and/or systems of care continue to be important factors in TIA outcomes in contemporary practice.

Implementation of best evidence TIA management requires organised systems of care. Although many hospitals in many countries have stroke units and acute neurovascular clinics, equipped with modern diagnostic facilities and specialist staff to provide optimal care, delays in seeking medical help and delays in management will likely be continuing to have a negative impact on TIA outcomes even in such systems.(20) It is important that patients understand the symptoms of TIA and the health practices make a correct diagnosis and initiate treatment urgently.

Implications for further research

The processes of care and outcomes of TIA patients can be improved by having optimal infrastructure. In many settings, such a highly specialised care system, with specialised personnel and availability of advanced technologies outside of a research setting, is not feasible.(21)

Prehospital care after a TIA plays an important role in primary health care settings. Managing TIA patients effectively in primary health care settings is of prime importance, as most of the patients seek initial help from their primary care physicians. General practitioners (GPs) have a role in managing TIA.(21) System delays however can result in many patients presenting to GPs not receiving appropriate care within guideline-benchmarked timeframes.(21, 22) Future research could evaluate models of integrated GP-specialist care utilizing, for example, telemedicine (which has proven effective in acute stroke care).

Conclusion

We hypothesised that the prognosis of TIA patients in studies reported in the years post-2007 will be improved compared to studies reported prior to 2008. We found that the prognosis of TIA patients is more favourable in the modern health care settings. This may reflect improvements in service models for TIA patients' care; with research evidence being translated promptly (though not always completely) into clinical practice.

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Figure legends

Table 1: Study specific stroke risk

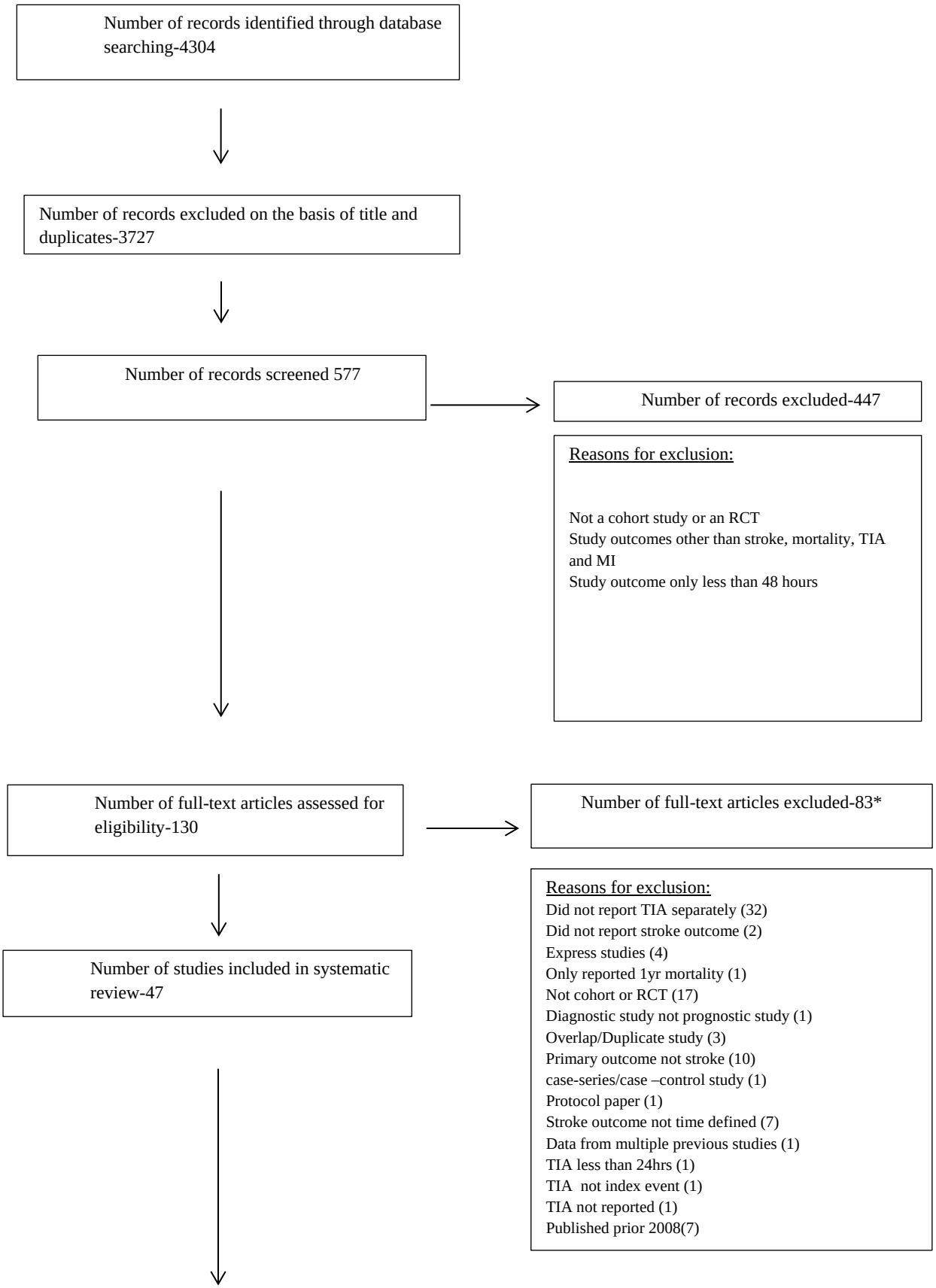
Figure 1: PRISMA 2009 Flow Diagram

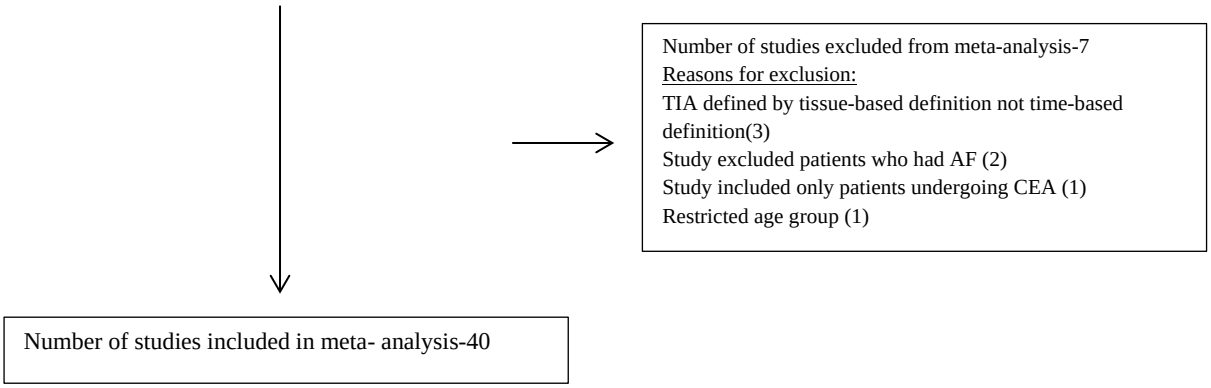
Figure 2: Cumulative risk of stroke pooled over 40 studies

Table 1: Study specific stroke risk

Time point	Cumulative risk of stroke	95% credible interval	I^2
2 days	0.012	0.006,0.022	0.87
7 days	0.034	0.02,0.055	0.93
30days	0.05	0.029,0.082	0.95
90 days	0.074	0.043,0.124	0.96

Figure 1: PRISMA 2009 Flow Diagram





*May not add to 83 because of more than one reason of exclusion

Figure 2: Cumulative risk of stroke pooled over 40 studies